APPENDIX 2

APPENDIX 2: PROTECTION FACTOR A PROTOCOL

PROTOCOL

DETERMINATION OF THE STATIC UVA PROTECTION FACTOR (Protection Factor A)

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OBJECTIVE

To determine the static UVA Protection Factor (PFA) for Sunscreen formulas.

SUBJECT SELECTION

A. Inclusion Criteria

1. Sex: male and female

2. Age: 10 to 65 years

3. Skin Type and Sunburn and Tanning History: Must be either skin type I, II or III as defined in the proposed monograph for SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN DRUGS, Federal Register of August 25, 1978 (43 FR 38206-38269).

4. Female subjects must wear a shirt on day 2 of the study that allows exposure of the back from the shoulder blades to the beltline.

5. General Condition: Must be in generally good health as determined from a brief medical history interview with emphasis on the effects of sunlight on their skin.

6. Informed Consent: Must be capable of giving informed consent.

B. Exclusion Criteria

1. Past history of phototoxic, photoallergic, or other abnormal responses to sunlight.

2. Allergies or sensitivity to cosmetic products, toiletries, sunscreens (i.e., Padimate O, PABA, oxybenzone, or octyl methoxycinnamate) and/or topical drugs.

3. Pre-existing or dormant dermatological conditions (e.g., severe acne, psoriasis, eczema, etc.).

4. Subjects with diabetes, Addison's disease, or thyroid conditions.

5. Subjects on chronic medication (e.g., steroidal and nonsteroidal anti-inflammatory drugs, insulin, antihistamines, antihypertensives, antibiotics (especially tetracycline, declomysin, chlorpromazine), or any medication known to cause abnormal responses to sunlight exposure.

6. Presence of sunburn, suntan, scars, active dermal lesions, and/or uneven skin tones on the areas of the back to be tested. Areas containing nevi, blemishes, or moles will not be used. Excess hair on the back is acceptable if the hair is clipped or shave.

7. Participation in any other clinical study (i.e., dermal patch, use tests, etc.) during the period required to complete this study.

NUMBER OF SUBJECTS

A minimum of ten (10) subjects will be required to complete the study. Any subject who is admitted into the study but who subsequently is determined not to meet the admission criteria will be terminated from the study and replaced by an eligible subject.

DURATION OF THE STUDY

The length of the study for each subject will be three (3) days.

DESIGN OF THE STUDY

This will be a controlled, randomized study.

RANDOMIZATION AND SUBJECT NUMBERING

Subjects entered into the study will have their initials entered sequentially on the Subject Assignment Sheet. The randomization of the application of the test products to the areas of the subject's back will be indicated on this sheet.

PROCEDURE

A. Pre-Study

Before being entered into the study, the subjects will be pre-screened by the investigator for the criteria indicated in the Subject Selection section. Only subjects who meet the requirements of this section, have signed an informed consent according to 21 CFR, Part 50 (see Appendix A for basic elements of a consent form), and have given an appropriate medical history will be entered into this study.

B. Light Source

The source of radiation will be a Xenon arc solar simulator having a continuous emission spectrum in the UVA (320 to 380 nm) region with less than 1 % of its total energy contributed by wavelengths below 320 nm. The lamp will be filtered with a WG335 filter, 3mm in thickness or equivalent. There will be less than 2% of erythemal effectiveness of the source contributed from wavelengths lower than 320nm and no more than 10% of the total output of the lamp will be visible and infrared radiation. The maximum intensity at the point of skin exposure must be less than 150 mW/cm2 total irradiance, as measured by a calibrated thermopile.

C. Minimal Response Dose (MRD) Determination

On day 1 of the study, a minimal response dose (MRD) for unprotected skin will be determined for each subject by irradiating five (5) one centimeter subsites on the lower back. The dose interval selected for the irradiation of the subsites shall be a geometric series wherein each exposure dose interval is 25% greater than the previous exposure. This geometric series is represented by 1.25 X n where n is the previous exposure dose.

For subjects of unknown sensitivity, the dose series will be 10, 12.5, 15.6, 19.5, and 24.4 J/cm2. For subjects with predetermined UVA MRD values, the dose series will be centered around the previously determined MRD.

After the exposure is completed, all immediate responses will be recorded. These include immediate darkening or tanning, immediate erythema, whealing, edema or flaring at the irradiation site. Subjects exhibiting the last three (3) responses will be disqualified from the test procedures.

After the immediate responses are recorded, the subjects will be instructed to shield the exposed areas from further UV exposure. Sixteen (16) to twenty-four (24) hours after the UV exposure, the five (5) subsites will be graded using the scale indicated in the Clinical Measurements section. The subsite with the lowest exposure dose showing a minimally perceptible tanning or erythema response will be selected as the MRD. The unprotected MRD will be reconfirmed on the day the test products are evaluated.

D. PFA Determination

1. Application of Test Products: Using a permanent marker, each subject will have six (6) 4 cm diameter circular test areas drawn on the back between the beltline and the shoulder blades and lateral to the midline. Five (5) of the four (4) test areas will be for the test products and the remaining one (1) will be used for the MRD. Following the randomization indicated on the Subject Assignment Sheet, 100 mg of Sunscreen formula will be applied to the appropriate test area and spread over the entire area using a finger cot.

In the same manner, 100 mg each of Sunscreen formulas will be applied to the designated test areas. The test areas are allowed to dry for twenty (20) minutes. During this period, the subjects should be instructed not to touch their backs against any surface.

2. Irradiation of the Static PFA Test Areas: While the test areas are drying, the solar simulator exposure doses required for Sunscreen formulas will be calculated based on the MRD of the subject and the expected PFA value of the sunscreen.

Each 50 cm2 test area will contain five (5) subsites that will be irradiated. The dose intervals selected for the subsites shall be a geometric series in which each exposure dose (subsite) is 25% greater than the previous exposure dose (1.25 x n). For example, if the subject's unprotected MRD is 10 J/cm2 and the expected PFA of the sunscreen is 2, then the central exposure interval (third subsite) will be 10 X 2 or 20 J/cm2, respectively. At the completion of the exposure at each subsite, opaque foil will be placed over the site to prevent further exposure.

Sixteen (16) to twenty-four (24) hours after irradiation, all subsites in the test areas will be graded for responses using the scale indicated in the Clinical Measurements section and the PFA values will be determined.

CLINICAL MEASUREMENTS

Sixteen (16) to twenty-four (24) hours after irradiation, all subsites in the test areas will be graded for responses using the scale indicated below. The person performing the grading will be unaware of the identity of the treatments applied to the test areas. To accomplish this, an additional person will record the scores on the subject evaluation forms. After completion of the grading, both the grader and recorder will initial the form.

0 = No reaction
0.5 = Minimal tanning or erythema, barely perceptible
1 = Light brown or red color with definite borders 1
1.5 = Medium brown or red, well-defined
? = Dark brown or red with edema

The lowest dose subsite showing a minimally perceptible response (0.5) will be selected as the MRD value. The PFA of the sunscreen is the ratio of the exposure dose for the protected MRD divided by the dose for the

unprotected MRD (PFA = protected MRD/unprotected MRD).

MATERIALS AND SUPPLIES

A. Test Product

CTFA will provide sunscreen formulas in coded containers (see Appendix 1).

B. Labeling

The containers will be labeled with an identifying letter and an SPF value.

MANAGEMENT OF INTERCURRENT EVENTS

A. Departure from Protocol

When a situation occurs which requires a departure from the protocol, the investigator will contact the study monitor. Contact with the study monitor will be made as soon as possible in order to discuss the situation and agree on an appropriate action. The Subject Report form and the final report will describe the departure from the protocol and the circumstances requiring it.

B. Adverse Events

Adverse experiences are defined as any unwanted signs or symptoms which in any way may be related to the product. All such experiences are to be entered on the Subject Report form with regard to severity, onset date, duration, and action taken.

Severe unexpected adverse events which are associated with the use of this product must be reported to the Sponsor.

Add adverse events,* regardless of severity or the cause/effect relationship, are to be recorded on the Adverse Reaction form and are to be noted as mild, moderate, or severe according to the following definitions:

Severe:	Incapacitating with inability to work or do usual activity
Moderate:	Discomfort enough to cause interference with usual activity
Mild:	Awareness of sign or symptom, but easily tolerated

*Expected events such as erythema, edema, and/or tanning in the test area are not to be coded as Adverse Experiences.

C. Concurrent Medication

No topical product (toiletry or medication) can be applied to the test areas. Medications excluded are indicated in the Subject Exclusion Criteria. Any concurrent medication taken during the study must be recorded on the Subject Evaluation Form.

D. Concurrent Illness

A concurrent illness is defined as any pre-existing or incurred illness, condition, or pathology for which there is no reason to assume that it has any relationship to or consequence of the test product being administered. Any concurrent illness must be entered on the Subject Evaluation Form.

E. Dropout Subjects

Reasons for subject removal from this investigation may include occurrence of any adverse event, significant protocol violation, noncompliance, subject's request, or the development of an intercurrent illness which puts the subject at risk or invalidates the results of the study. A genuine effort must be made to determine the reason why a subject fails to complete or is dropped from the study. This information must be reported on the Subject Report form.

F. Rejection of Test Data

The test data shall be rejected if the exposure series fail to elicit an MED response on either the treated or unprotected skin sites or if the responses on the treated sites are randomly absent, indicating that the product was not spread evenly.

G. Modification of the Protocol

Neither the investigator nor CTFA will modify this protocol without obtaining the concurrence of the other. The party initiating a modification will confirm it in writing.

INSTITUTIONAL REVIEW BOARD APPROVAL

The investigator assures that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 of FDA regulations will be responsible for the initial and continuing review and approval of this clinical study. A copy of the formal written notification of approval of the protocol and consent form and a copy of the IRB approved informed consent form will be submitted to the sponsor prior to the start of this study. It is also necessary to submit the name and address of the IRB and a list of IRB members and their titles, occupations, and institutional affiliations.

The investigator also assures that he/she will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects. No changes in the research requiring IRB approval will be made until the IRB has approved the changes, except where necessary to eliminate immediate hazards to human subjects. Documentation of the approval must be forwarded to CTFA for any amendment requiring IRB approval. The investigator must also report to his/her IRB within 3 months after completion, termination, or discontinuation of the study.

REPORTING REQUIREMENTS

It is understood that this investigation will be conducted in accordance with the basic Investigator/Sponsor contract drawn up by CTFA.

SUBJECT EVALUATION FORMS

Subject evaluations are provided for each study subject. They will be provided by the sponsor and completed by the investigator. All data and information on these forms are to be typed or legibly printed in black ink and signed by the investigator, and dated as of the date of signature.

Corrections of data on the Subject Evaluation forms can only be made by crossing out the incorrect data (in such a manner that it leaves the previous entry identifiable) and writing the correct values next to those crossed out. Each correction must be initialed and dated by the individual making the correction.

If any changes are made to a Subject Evaluation form after it has been signed and dated by the investigator (e.g., corrections or new data entered in an area previously blank), the entry must be initialed and dated by the individual making the entry. If that individual is not the investigator, the investigator must initial and date each page that was changed to indicate awareness and agreement with the change.

ON-SITE MONITORING/AUDITS

The study will be monitored by CTFA through site visits and frequent communications (telephone, letter, fax) to insure that the investigation is conducted according to the protocol and to assist in resolving any difficulties encountered while the study is in progress.

The investigator agrees that CTFA, its employees or agents, or its constituent members will have the right from time to time during the course of this study to audit and review pertinent medical records relating to the clinical evaluation.

The United States Food and Drug Administration, in the person of a trained and properly authorized employee of the department, may request access to all study records, including source documents, for inspection and copying. Similar auditing procedures may also be conducted by a representative of CTFA's Regulatory Department.

STATISTICAL ANALYSIS

The contract laboratory will perform the following calculations for each of the products tested:

Mean Static PFA
Standard Deviation
Standard Error
Five Percent of the Mean

RECORD RETENTION

Federal law requires that all Subject Evaluation forms and a copy of all records (e.g., informed consent forms, source documents, test article dispensing records, etc.) which support subject evaluation forms of this study, must be retained in the files of the responsible investigator for a period of 2 years. If the responsible investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody may be transferred to a person who will accept the responsibility. CTFA must be notified in writing of the name and address of the new custodian.

APPENDIX A

BASIC ELEMENTS OF A CONSENT FORM

Federal regulations require that written informed consent must be obtained from each subject before being entered into the study.

The minimum requirements necessary to such consent should include the following information:

1. An explanation of the scope, aims, and purposes of the research, the procedures to be followed, and the expected duration of the subject's participation.

2. A description of all reasonably foreseeable risks or discomforts to the subject.

3. A description of any benefits to the subject or to others that may be reasonably expected from the research.

4. A disclosure of appropriate alternate procedures or courses of treatment, if any, that might be advantageous to the subject.

5. An offer to answer any questions a subject may have about the research, subject's rights, or related matters.

6. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

7. A statement indicating that medical records will be made available to the sponsor and describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

8. An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained.

9. An explanation of whom to contact for answers to pertinent questions about the research and whom to contact in the event of a research-related injury to the subject.